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Transplacental Transport of Lead

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Neurotoxicity is the major health effect from exposure to lead for infants and young children, and there is current concern regarding possible toxic effects of lead on the child while *in utero*. There is no placental-fetal barrier to lead transport. Maternal and fetal blood lead levels are nearly identical, so lead passes through the placenta unencumbered. Lead has been measured in the fetal brain as early as the end of the first trimester (13 weeks). There is a similar rate of increase in brain size and lead content throughout pregnancy in the fetus of mothers in the general population, so concentration of lead probably does not differ greatly during gestation unless exposure of the mother changes. Cell-specific sensitivity to the toxic effects of lead, however, may be greater the younger the fetus. Lead toxicity to the nervous system is characterized by edema or swelling of the brain due to altered permeability of capillary endothelial cells. Experimental studies suggest that immature endothelial cells forming the capillaries of the developing brain are less resistant to the effects of lead, permitting fluid and cations including lead to reach newly formed components of the brain, particularly astrocytes and neurons. Also, the ability of astrocytes and neurons to sequester lead in the form of lead protein complexes occurs only in the later stages of fetal development, permitting lead in maturing brain cells to interact with vital subcellular organelles, particularly mitochondria, which are the major cellular energy source. Intracellular lead also affects binding sites for calcium which, in turn, may affect numerous cell functions including neurotransmitter release.

Introduction

Life *in utero* as a developing embryo and fetus may be the most vulnerable period for lead toxicity to occur. It is clear from research that has been reported in the past few years that neurotoxicity from lead occurs from exposure to levels not previously thought to be toxic (*1–4*) and that the perinatal period may be a particularly vulnerable time for neurotoxicity to occur (*5,6*). However, a number of specific questions need to be further addressed such as the mechanisms and factors affecting transplacental transport of lead from mother to fetus, possible effects on normal placental function, and, finally, the affinity of lead for the developing nervous system and the nature of early biochemical or pathological effects.

The information currently available to answer these questions is limited (*7,8*). The placenta is generally described as the interface between the mother and the outside world or environment and the developing fetus. Substances cross the placenta by a number of transport mechanisms as in other body tissues, simple diffusion for small molecules, activated transport for larger molecules with molecular weight less than 400,000, and pinocytosis for macromolecules. The principal function, of course, is to provide a conduit for the nourishment of the developing fetus. The placenta has mechanisms that enhance the transport of those substances that are needed and restricts the entry of those substances that are toxic or otherwise harmful. These mechanisms are related to hormonal influences, some oxidative reactions, mostly nonenzymatic, and perhaps, most importantly, umbilical cord or fetal blood flow. The placenta provides a route for excretion of toxic wastes. This is, admittedly, a simplistic view, but it is in this context that the role of the placenta in fetal exposure to lead needs to be considered. Most studies to date have concerned essential organic nutrients and macromolecules. Pharmacologists have understandably a large interest in drug and chemical metabolism in the placenta, but there has been relatively little study to date of the mechanisms for transport of essential trace metals apart from calcium and iron and very little study of transplacental transport of toxic metals *per se,* including lead, cadmium, and mercury.

The purpose of this paper is to provide an overview of the mechanisms for transplacental transport of lead and factors that may influence it. There is also need to comment on possible experimental models for further study of lead effects *in utero.* The availability of human fetal tissue for research is very limited, and there is no ideal animal surrogate. The primate might be the best choice for obvious reasons, but here there are constraints; high cost is a major concern. For this reason the rat may be a satisfactory alternative, at least in terms of studying mechanisms of transport and some aspects of intrauterine toxicity.

The fetal-maternal barrier in the mature rat placenta is very similar anatomically to that of the human placenta (Fig. 1) (*9*). Both are hemochorial placentas, that is, the fetal chorionic villi bathe in lacunae of maternal blood (Fig. 2). In the human placenta, the villous capillary is separated from maternal blood by three layers or cells, the capillary endothelial cell, an interstitial or connective tissue layer, and a layer of cytotrophoblasts. Syncytiotrophoblasts do not form a continuous layer but are intermittent. The layers of the chorionic villus in the rat are similar but differ by the

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presence of an additional layer of cytotrophoblasts. The photomicrograph in Figure 2 shows the relationship of fetal capillaries to endometrial tissue which contains a rich capillary bed opening into lacunae of maternal blood. In Figures 3 and 4 and the ultrastructural components of the cells composing the chorionic villus can be seen. Intracellular vacuoles functionally involved in transport of nutrients and macromolecules are common to endothelial cells, cytotrophoblasts, and syncytiotrophoblasts.

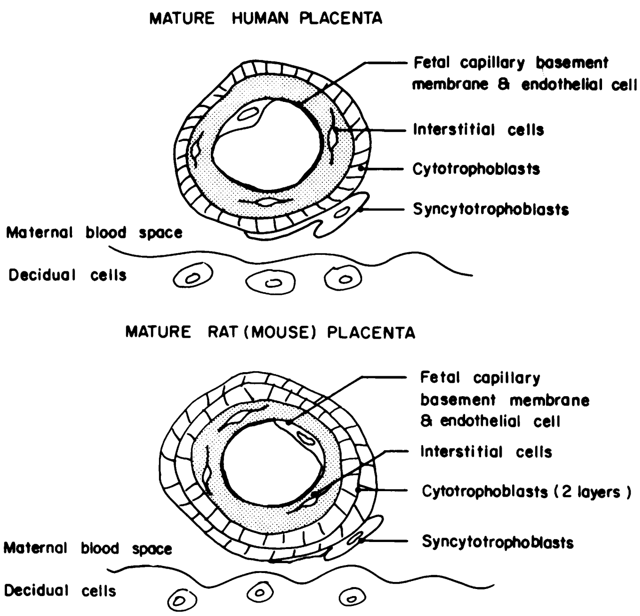

FIGURE 1. Comparison of chorionic villus of mature human placenta and rat placenta. The fetal maternal-barrier in the human chorionic villus consists of three layers of cells, fetal endothelial cells, interstitial cells, and a single layer of cytotrophoblasts. The outer syncytiotrophoblasts do not form a complete layer. The rodent (rat or mouse) chorionic villus differs in that it contains two layers of cytotrophoblasts. Both human and rodent chorionic villi bathe in lacunae of maternal blood. The endometrial basal plate is characterized by decidual cells as well as maternal blood vessels.

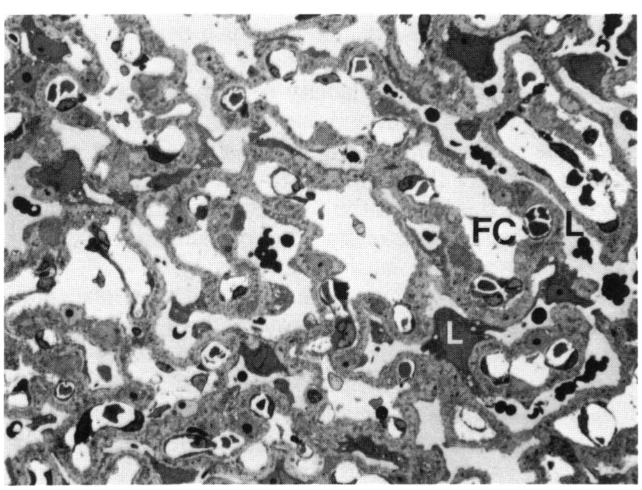

FIGURE 2. Light microscopic photograph of Figure 3. Mature rat placenta showing fetal capillaries (FC) in villi within lacunae (L) of maternal blood.

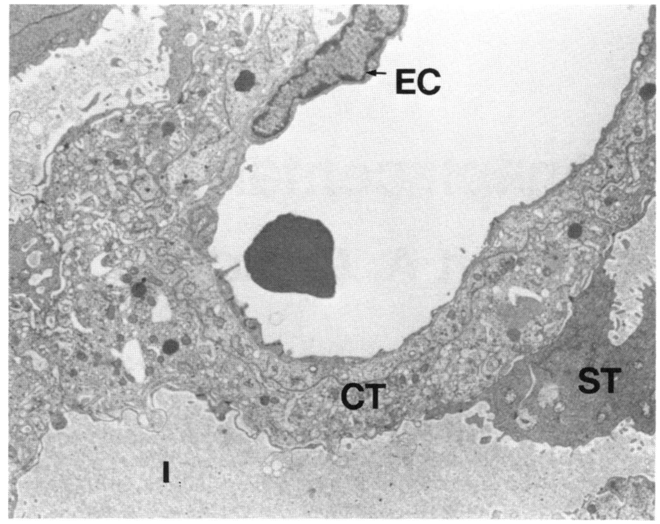

FIGURE 3. Low magnification electron photomicrograph of mature rat placenta showing lumen cell layers of chorionic villus, endothelial cell (EC), cytotrophoblasts, syncytiotrophoblasts (ST), and maternal lacunar space (L).

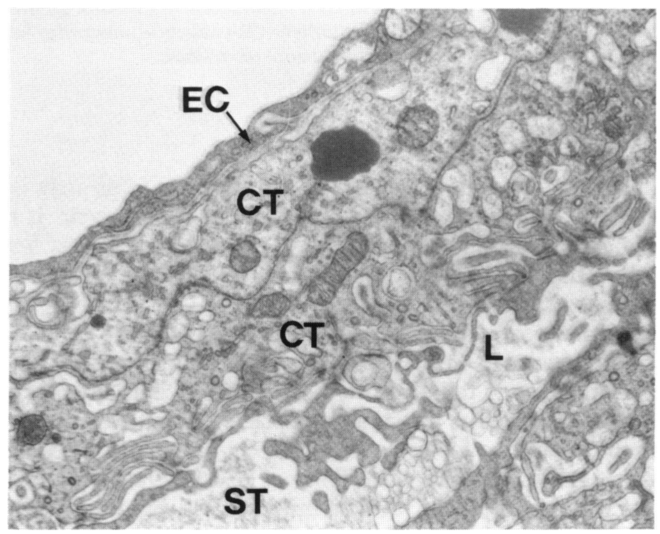

FIGURE 4. High magnification electron photomicrograph of rat placenta showing a thin layer of endothelial cells (EC), cytoplasm lining the villous capillary, two layers of cytotrophoblasts (CT), and a narrow irregular portion of syncytiotrophoblast (ST) lining maternal lacunar (L) blood space.

Electron microscopic studies and immunohistochemical analyses have demonstrated that the cytotrophoblast is primarily the germinative cell layer, whereas the syncytiotrophoblast is the secretory layer as evidenced by hormone content (steroid and peptide hormones) and the numerous mitochondria as energy source to support the high level of metabolic activity as well as transport function (*9*). The syncytiotrophoblast has been shown to be the site of metallothionein synthesis, a protein that binds cadmium and may also enhance transport of the essential trace metals zinc and copper (*7,10*).

Table 1. Transplacental transport of toxic metals.

Metal	Number of samples	Blood levels: Mother	Blood levels: Cord	Reference
Lead, ng/mL	19	40.4 ± 18.2	37.1 ± 13.5	(*11*)
		76.1 ± 23.5	67.7 ± 41.0	(Nakano and Kuroso, unpublished)
		64.8 ± 18.8	58.4 ± 20.2	(*12*)
Cadmium, ng/mL	19	1.1 ± 0.9	0.4 ± 0.2	(*11*)
Total mercury, ng/mL	231	19 ± 36	30 ± 62	(*13*)
Methyl mercury, ng/mL	226	9 ± 5	14 ± 9	(*13*)
Iron, ppm		234 ± 102	392 ± 166	(*13*)

Table 1 compares concentrations of toxic metals between mother's blood and cord blood levels for several metals. There have been several studies comparing maternal and fetal blood lead levels, some of the more recent are cited. All the studies show good maternal-fetal correlation (r = 0.77 to 0.80) with cord blood equal to or slightly lower than maternal blood lead levels. It appears, therefore, that there is no protective barrier for the fetus from exposure to lead from mother's blood. But for some metals the placenta is a barrier, and for others it seems to enhance transport. Cadmium may be 40 to 50% lower in fetal blood than in mother's blood, and the protective barrier is thought to be related to metallothionein binding. The newborn is relatively spared cadmium exposure and is usually born with a body burden of less than 1 mg. On the other hand, iron, an essential metal, is present in higher concentration in the fetal blood, suggesting preferential transport and affinity for the fetus. The higher level of total mercury and methyl mercury in fetal blood shown here is consistent with several other reports. Methyl mercury has a particular affinity for the nervous system, where it becomes concentrated and may be associated with prenatal mercury toxicity. It must be concluded, therefore, that each trace metal, whether toxic or essential, has its own transplacental transport mechanism. There are few, if any, generalities.

The mechanism for the transport of lead to the placenta is not well defined. There are several reasons for suggesting that lead transport may be a matter of simple diffusion from maternal to fetal circulation. For one, there is the close quantitative relationship between mother's blood levels and cord blood levels. There does not seem to be any placental barrier or enhancing mechanism. Secondly, the transfer of lead from mother to fetus has been shown in experimental models (guinea pig) to be linearly related to umbilical cord blood flow rate (*14*). As the fetus grows, the umbilical cord flow rate also increases. It has also been shown in the human placenta that as the fetus grows and the placenta matures, the number of villi increase by branching and the cross-sectional diameter of the villi decreases from about 170 μm early in gestation to about 40 μm near term. This process more than doubles the villus surface area from 2 m^2 to 11 m^2 at term (*15*), and at the same time fetal blood vessels become more excentric, and the syncytiotrophoblastic layer thins, so the distance between maternal and fetal blood vessels decreases. The percentage of fetal cardiac output that goes to the placenta is a constant 40 to 50% throughout gestation, so the volume of cardiac output per weight of fetus does not change greatly. The volume of cord blood flow is directly related to size of fetus (*16*). These observations are particularly relevant to assuring a constant flow of oxygen to the fetus as well as transplacental diffusion of lead from mother to fetus.

There are few measurements of lead levels in fetal tissues at different ages of gestation. The largest number of measurements in a single study were reported by Barltrop (*17*). An important question is how early in gestation does transfer of lead occur. The Barltrop study started with fetuses about 13 weeks of age and extended to term. There is no reason to believe transfer of lead does not occur earlier. This study showed that lead content of the brain and other tissues grows with the increase in organ size, but lead concentration changed very little (*17*). This was probably because maternal blood lead was relatively constant. The fetuses were from abortions from mothers in the general population.

Although the rat is probably the best-studied animal model to date regarding biochemical effects of lead on the brain, there are few studies to date regarding distribution of lead in the neonatal rat brain or effect on function. Behavioral effects have been demonstrated in rats with chronic post-weaning exposure to as low as 50 ppm of lead acetate in drinking water (*18*), but metabolic effects of lead on the central nervous system and its distribution have not been reported. Lead levels in the nervous system of rats intoxicated for the first 8 months of life by lead acetate (0.2% in drinking water) differed in various regions of the brain. Lead levels were highest in the hypocampus and cerebral neocortex (*19*).

There is also some experimental evidence to suggest that the fetal brain may have greater sensitivity to lead toxicity than the more mature brain. Rat pups readily develop encephalopathy during the first few days of life and resistance to lead-induced neurotoxicity occurs after 18 to 20 days of age (*20,21*). Holtzman and co-workers (*21*) propose that the development of resistance to lead encephalopathy is related to the formation of lead-protein complexes in astrocytes that sequester lead away from mitochondria. This role of lead-protein complexing is similar to that postulated in renal tubular epithelial cells as a mechanism for permitting the kidney to excrete lead without cellular toxicity (*22*). The lead-protein complexes or inclusion bodies are thought to contain a number of richly acidic proteins (*23*). More recently, Egle and Shelton (*24*) have identified the most abundant protein component of isolated inclusion bodies to be a constitutive protein of the central nervous system, most abundant in the cerebral cortex. In rat brain the protein was found to be developmentally regulated. Only traces were detected 3 days after birth, but within 1 to 2 weeks adult levels were achieved. These studies do suggest, therefore, that this cellular mechanism to sequester lead is not present in the fetal brain.

Experimental studies suggest that the immature endothelial cells forming the capillaries of the developing brain are less resistant to the effects of lead than capillaries from mature brains and permit fluid and cations including lead to reach newly formed components of the brain, particularly astrocytes and neurons (*25*). Recently, Markovas and Goldstein (*26*) investigated the effects of inorganic lead on calcium, phospholipid-dependent protein kinase (protein kinase C) in brain microvessels from 6-day-old rat pups. They found that micromolar concentrations of lead activate this enzyme to an extent equivalent to micromolar calcium, suggesting this may be a very sensitive mechanism for cellular toxicity in capillaries by lead, resulting in a breakdown in the normally tight blood-brain barrier.

Lead alters other calcium-mediated cellular processes (*27,28*) and may also be associated with transplacental transport of calcium. Barltrop (*17*) observed that femur lead increased rapidly in the third trimester, corresponding to onset of ossification and deposition of calcium. There is a question whether the increased deposition of lead in the femur along with calcium is due to some commonality between lead and calcium metabolism. Calcium deficiency does enhance lead absorption and the pathological effects of lead (*29*). The placenta does contain a calcium-binding protein identical to that present in the intestine (*30*). A recent comparison of placental transfer of toxic metals by Nakano and Kurosa from the Minamata Institute in Japan (unpublished communication) found that lead levels in the placenta were strongly correlated "with levels of elements related to bone metabolism suggesting that placental lead may be associated with calcification of this tissue."

Toxic effects of lead on placental function or morphology have not been documented, but with toxic levels of lead changes must occur. Lead has been used as an abortifacient, and toxicity results in miscarriages. In experimental animals including rats, toxic levels reduce the number of viable offspring, and offspring are smaller than normal (*31*). Placentas from lost fetuses are resorbed, but associated placental toxicity has not been studied.

There are several reports of placenta lead concentrations in the literature (*32–34*). Since the placenta is mostly maternal and fetal blood, it might be expected that the lead content would be equivalent to blood levels unless there are foci of concentration. But values in various reports are quite variable, mostly higher than blood values. There are two possible explanations of this. For one, there may, in fact, be a lead-concentrating mechanism in some component of the placenta, in trophoblasts for instance, but this has not been demonstrated, and from what is known about mechanisms for transplacental transport of lead, this is unlikely. A second explanation seems more likely, that lead is precipitated in the term placenta along with calcium. As villi age they become necrotic, scarred with fibrous tissue, and may contain foci of calcium deposition. This would provide considerable sampling variability, which may be another factor contributing to inconsistent findings.

An interesting set of values is provided in a paper by Khera and co-workers (*35*) concerning placenta lead values in women in lead industries. Normal placental levels of lead were found to be 0.29 $\pm$ 0.9 μg/g, whereas lead in placentas from stillborns was 0.45 $\pm$ 0.32 μg/g. Normals were defined as no occupational exposure to lead for the 2 years prior delivery. Nevertheless, these values are higher than the general population. Stillborns as a group were even higher, perhaps because of more calcium-lead precipitation in the placenta. Finally, as might be expected, increase in lead in the placenta was related to length of occupational lead exposure and age. Measurements of lead in amniotic fluid and fetal membranes are also quite variable and are, generally, higher than the placenta, but the significance of this, if any, is not known.

In summary, there is no apparent maternal-fetal barrier to lead. Fetal blood lead levels are nearly equal to maternal blood lead levels. The primary mechanism for transplacental lead transport is probably simple diffusion and is probably related to fetal blood flow rate. It is suggested, however, that fetal tissue levels may be influenced by calcium transport and intracellular calcium metabolism. On the other hand, lead may alter calcium-mediated cellular processes, producing toxicity.

Lead concentration of developing fetal tissues including the brain is related to the level of blood lead and is generally constant throughout fetal life. Lead content increases with brain size. There is currently no information, however, about changes in regional distribution of brain lead during development.

Fetal brain may be more susceptible to lead toxicity. The blood-brain barrier is immature and does not provide any barrier to lead entry into the brain. Also, there is some evidence that formation of lead-protein complexes, a mechanism for sequestering lead in mature tissues, is not functioning in fetal brain.

Finally, we must depend on animal model for estimating risk for intrauterine lead toxicity; data from human fetuses are not available. Primates are the best model for quantitative data; rats may be the most practical model for determining mechanisms of toxicity.

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